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Radical Diazidation of Alkenes: Cu/Fe/Mn Catalysis and Electrochemical Support

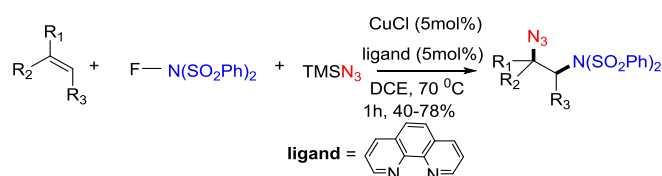
Nisar Ahmed*[a], Saira Khatoon[a] and Bahareh Shirinfar[b]

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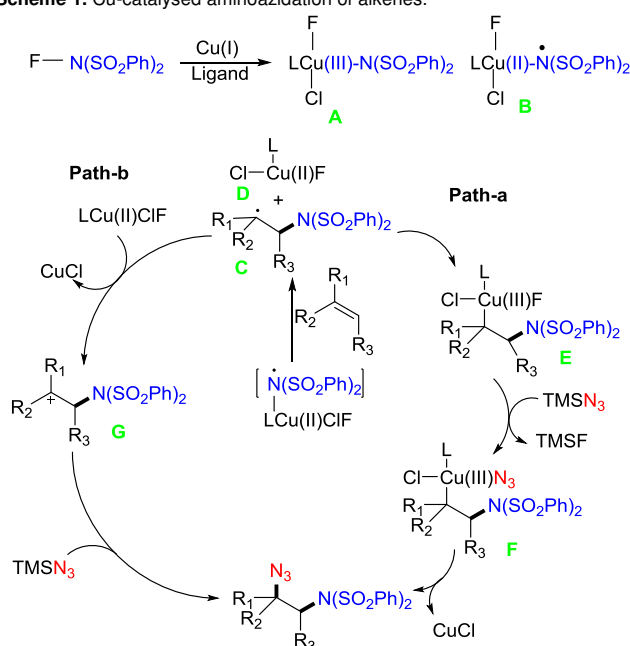
Vicinal diazides are important precursors for the synthesis of vicinal diamines, which constitute one of the most important functional motifs in organic chemistry, because of their presence in a variety of biologically active and pharmaceutical molecules and involvement in catalytic transformations.^[1] Despite their extensive utility, the development of a new method allowing efficient preparation of 1,2-diamine continues to be a stimulating challenge. To synthesise vicinal diamines, chemists generally expose alkenes to harsh chemical oxidants, which can produce environmentally toxic by-products.

The organic azides have gained attention due to their use in azide-alkyne cycloaddition,^[2] C-H bond amination,^[3] Staudinger ligation,^[4] and biological applications.^[5] Moreover, azides have been used in materials science,^[6] supramolecular chemistry,^[7] and nano-biotechnology.^[8] In most methods of diazide formations, stoichiometric heavy metals are used, which generally exhibit limited substrate scope.^[9] Recently, much attention has been paid to the diazidation of alkenes by using transition metals. To access diazide substrates, radical azidation of alkenes is catalysed generally by transition metals^[10,11] and particularly powered with electricity^[12] which generates considerable significance. The electrically catalysed organic reactions occur at the interface of electrodes (anode and cathode) and an electrolyte. These reactions serve as powerful methods for the synthesis of complex organic molecules, as they provide for an easy generation of highly reactive species, even under very mild conditions, and a consequent construct in green chemistry.^[13]

The work by Studer et al.^[10] outlines an approach of radical-mediated intermolecular vicinal aminoazidation for a series of terminal and few internal alkene derivatives catalyzed by copper (Scheme 1), which can easily be transformed into amine derivatives. This transformation resulted into corresponding aminoazides in moderate to excellent yields by using commercially available trimethylsilyl azide (TMSN₃) as N₃-source and N-fluorobenzenesulfonamide (NFSI) as a nitrogen-radical precursor. Moreover, excellent diastereoselectivity (>98:2) is reported for internal alkenes by using this protocol. Correspondingly, a plausible reaction mechanism based on the reported processes is outlined in Scheme 2. First, the reduction of NFSI by CuCl provides Cu (III) species **A** in equilibrium with Cu (II) N-centered radical **B** and both act as bis-sulphonylamidyl radical source. The addition of species **A** or **B** to alkene prompts a radical **C**, which is proposed to follow either (a) path-a, wherein **C** radical is trapped by **D** Cu(II)-species and changed to **E**-species, this **E** species experiences ligand exchange with TMSN₃ to produce Cu(III) complex **F** which on reductive elimination is furnished to the desired aminoazide derivative, or (b) path-b in which **C** species undergoes oxidation to an intermediate cation **G**, this cation intermediate **G** trapped by TMSN₃ and outcomes as aminoazide derivative.



Scheme 1. Cu-catalysed aminoazidation of alkenes.

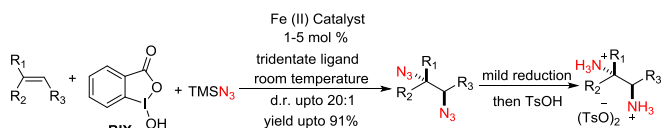


Scheme 2. Plausible mechanism for Cu-catalysed aminoazidation of alkenes

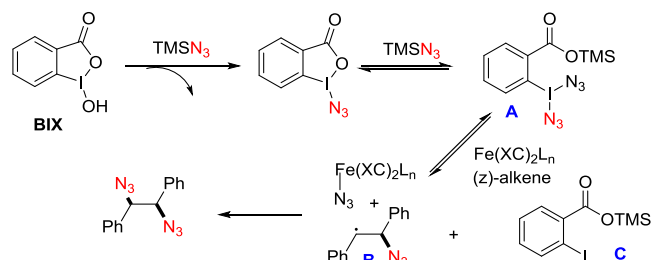
In 2015, Xu and co-workers achieved a convenient approach for diastereoselective (>20:1) diazidation of olefins, which was catalysed by iron with low catalyst loading (1-5 mol%) at room temperature (Scheme 3).^[11] They explored the scope of this reaction with good yields for a wide range of unfunctionalized, highly functionalized and dense alkene systems. The mechanistic studies after carrying out different control experiments of diazidation suggest a plausible reaction mechanism outlined in Scheme 4. The benziodoxole (BIX) is converted to intermediate **A** by the successive substitution and addition with TMSN₃. In the presence of an iron catalyst, the I-N₃ bond of intermediate **A** reductively cleaves and generates an azidoradical **B** of alkene and releases intermediate **C**. It is likely that the high valent iron species **B** further oxidizes and yields diazide. Moreover, this method offers an approach to the synthesis of vicinal primary diamines.

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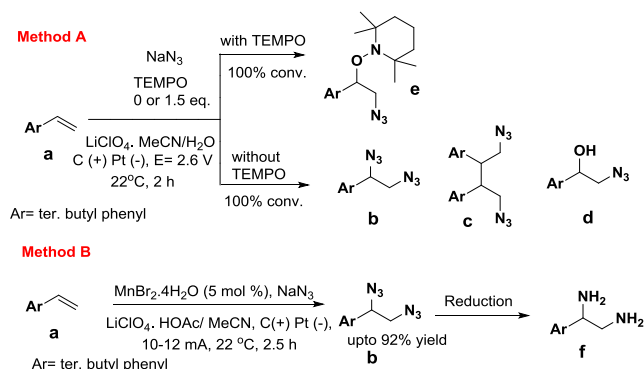


Scheme 3. Fe-catalysed diazidation of alkenes



Scheme 4. Plausible mechanism for Fe-catalysed diazidation of alkenes by using BIX.

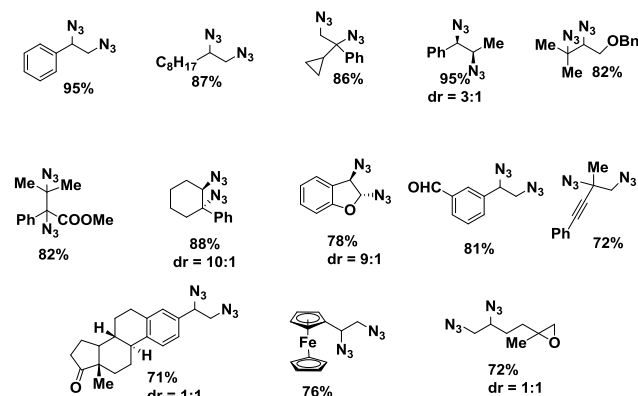
The Schäfer's group reported the oxidative addition of the azide ion to olefins, in the absence of metal salts. However, low yields of 1,2-diazides were observed.^[14] Lin *et al.* developed a handy method to form C–N bonds by pairing manganese catalysis with electrochemical azide oxidation in the presence of alkenes.^[12] A key advantage of the electrochemical approach is the tunable accuracy of its oxidizing power, which leaves other sensitive substituents such as alcohols and aldehydes intact. During the experiment, the reaction proceeded over several hours at room temperature, forming hydrogen at the counter electrode as a gentle by-product. The reaction was catalyzed by earth abundant Mn^{II} as redox active catalyst in the electrochemical cell. Lin *et al.* enlightened the critical role of the catalyst in the modulation of radical reactivity, by conducting the reactions without catalyst and found <5% of 1,2-diazidation along with homo-couplings and over-oxidation products on full consumption of starting material (Scheme 4, Method A); while on the other hand use of catalyst resulted in up to 98% yields of relative diazidation products. The optimal protocol involved: manganese(II) bromide (MnBr₂) as electrochemical-catalyst, acetic acid (AcOH) as proton source, reticulated vitreous carbon (RVC) as an anode, platinum as a cathode, all in the 0.1 molar solution of lithium perchlorate (LiClO₄) in acetonitrile under the inert atmosphere of nitrogen. Along with 3 eq. of sodium azide (NaN₃) the current of 10–12 mA applied for 2.5 h resulted in the formation of up to 92% isolated yield of 1,2-diazide product (Scheme 5, Method B).



Scheme 5. Diazidation in the absence (Method A), and presence (Method B) of Mn-catalyst.

This electrochemical protocol for diazidation proceeds

under mild conditions and it shows high reactivity and excellent chemoselectivity. This methodology is applicable to the diazidation of various alkenes with different functional groups and substitution pattern. These electrochemical diazidation reactions were conducted at the oxidation potential of the catalyst-azide adduct (~0.62 V), which is below that of many oxidation-sensitive functionalities, thus showing little evidence of undesired side reactions. Lin *et al.* applied this protocol very efficiently to the formation of 1,2-diazides for a wide range of substrates such as aryl substituted acyclic alkenes, long range of activated and unactivated alkenes, terminal, 1,2 and 1,1-disubstituted, tri, tetra-substituted hindered alkenes, cyclic alkenes, electron rich heterocyclic systems i.e. benzofuran, N-tosyl indole, oxidation sensitive functionalities i.e., aldehydes, alcohols, ketones, sulfides, amines and alkynes, which are some of the examples mentioned in Scheme 6. Lin *et al.* have indicated that the formation of Mn-azide adduct during the reaction played a central role in inhibiting competing side reactions, thus enhancing chemoselectivity. During these transformations, they used NaN₃ as the azide source, which is readily available and exhibits markedly lower toxicity and volatility, compared to other azide derivatives. Moreover, this methodology has various advances: it showed little reliance on the electronic properties of the aryl substituent for diazidation. Due to steric hindrance, tetra-substituted alkenes remain notoriously challenging to functionalise, and no methods exist for the direct diazidation or diamidation of such substrates. In comparison, this method offers convenient access to 1,1,2,2-tetra-substituted vicinal diamines in outstanding yields. Thus, this method was applied to substituted cyclic alkenes, which gave the trans-1,2-diazides predominantly, and electron-rich heterocycles which formed diazides with high diastereoselectivity. Further, the successful reduction by Lin *et al.* of diazide derivatives to vicinal diamines in a single step with high chemoselectivity and excellent yields, represents an efficient and atom-economical synthetic approach.



Scheme 6. Scope for electrocatalytic diazidation of alkenes.

Furthermore, Lin and co-workers suggested an interesting mechanistic approach of bicyclic Mn-assisted transfer of two equivalents of azidyl radical to olefins leading to diazidation. Initially from the data of ultraviolet-visible spectroscopy, they inferred that Mn(II)-N₃ formed through ligand exchange between NaN₃ and Mn(II)-X(X, Br or OAc) which on subsequent oxidation at anode form Mn(III)-N₃. Mn(III)-N₃ acts as a key intermediate for azidyl radical transfer to alkene substrates (See Figure 1).

Overall, the synthetic routes for C–N₃ bond formation through a radical mechanism by using transition metals^[10–12] provide efficient diazide products, which can be further applied in many transformations to synthesise various valuable nitrogen-containing compounds of pharmaceutical interest. The catalytic

protocols developed by Studer et al.^[10] and Xu et al.^[11] were dependent on azidotrimethylsilane (TMSN₃) as N₃-source, which

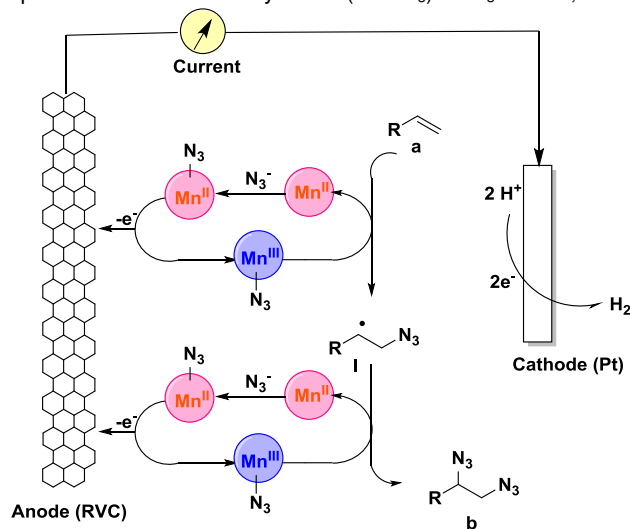


Figure1. Lin *et al.* proposed mechanism of electrocatalytic alkene diazidation.

is a toxic and volatile reagent. However, the method of Lin *et al.*^[12] is demonstrated to be environmentally friendly, very simple and highly efficient for 1,2-diazide derivatives and this synthetic strategy is a smart alternative for easy access to 1,2-diamines, which can be used for the future modern syntheses. Moreover, the diazidation and reduction procedures could be carried out consecutively without elegant isolation of the intermediate, thereby establishing a general, safe, and operationally modest method for vicinal diamine synthesis.

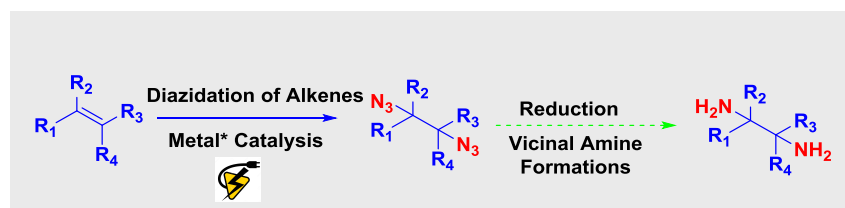
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Keywords: diazidation • electrosynthesis • vicinal amines • terminal alkenes • transition metals

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Radical Diazidation of Alkenes: Cu/Fe/Mn Catalysis

The synthetic routes for C- N_3 bond formation through a radical mechanism with the use of transition metals provide efficient diazide products, which can be further applied in many transformations to synthesise various valuable nitrogen-containing compounds of pharmaceutical interest. The reported methods evidence stoichiometric heavy metals and toxic reagent (as N_3 -source) and generally exhibit a limited substrate scope. However, the electrochemical diazidations are found to be environment- friendly and very simple, while also providing a highly efficient way to synthesise 1,2-diazide derivatives. Further, they provide a smart alternative for easy access to 1,2-diamines, which can be used further for future modern syntheses.